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Brief Report

Disruption of latent inhibition to a contextual stimulus with systemic amphetamine

C. Norman* and H.J. Cassaday

Institute of Neuroscience, School of Psychology, University of Nottingham, University Park, Nottingham NG72RD, UK

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Abstract

This experiment examined the effects of 0.5 and 1.5 mg/kg doses of amphetamine (AMP) in male Wistar rats, on conditioning to a contextual stimulus that for half the animals has been pre-exposed, in an appetitive conditioning procedure. Amphetamine was administered during both pre-exposure (3 days) and acquisition (15 days). Latent inhibition (LI, reduced conditioning in pre-exposed relative to non-pre-exposed rats) was seen in controls but not at either AMP dose. This abolition of LI was seen under AMP at two levels of responding in acquisition and confirmed in drug free extinction. It suggests that, like conditioning to discrete stimuli, conditioning to contextual stimuli is subject to LI and can be disrupted by AMP.

Keywords: Latent inhibition; Amphetamine; Contextual conditioning; Rat

In latent inhibition (LI), conditioning to a stimulus is retarded by previous exposure to that stimulus without consequence. Amphetamine (AMP) has been shown consistently to abolish LI to discrete stimuli, in aversive procedures (Solomon et al., 1981; Weiner, 2003; Weiner & Feldon, 1997; Weiner, Lubow, & Feldon, 1981; Weiner et al., 1997; for reviews); and reduced LI in an appetitive procedure (Killcross, Dickinson, & Robbins, 1994). Whilst LI to contextual stimuli has previously been demonstrated in normal animals (e.g., Kiernan & Westbrook, 1993; Killcross, Kiernan, Dwyer, & Westbrook, 1998), the effects of AMP on LI to a contextual stimulus have not been directly tested.

In a standard trace conditioning procedure, we have previously presented evidence of increased conditioning under AMP to a contextual stimulus (flashing lights) presented continuously during (trace) conditioning to a discrete stimulus (Norman & Cassaday, 2003). The procedure was to present the flashing lights for the whole conditioning session and to superimpose pairings of the (trace conditioned) discrete stimulus and footshock. Thus, the continuously presented contextual stimulus may have been subject to LI, due to its presentation without consequence prior to pairings of the discrete stimulus and footshock. On this account, the increased conditioning to the experimental background stimulus seen under AMP (Norman & Cassaday, 2003) may have been a result of AMP disruption of LI to this contextual stimulus.

Based on the evidence that AMP disrupts LI to discrete stimuli and the possible disruption by AMP of LI to a contextual stimulus described above, this current study examines whether AMP disrupts LI produced by pre-exposure to a contextual stimulus.

An appetitive conditioning procedure was used here to allow us to test AMP effects over the course of acquisition (on-the-baseline) as well as in extinction (off-the-baseline). The contextual stimulus was provided by a continuously presented flashing light stimulus that for half the animals has previously been pre-exposed. Conditioning in pre-exposed (PE) groups was compared with non-pre-exposed (NPE) groups and it was predicted that AMP would disrupt LI, seen as increased

* Corresponding author. Present address: School of Biomedical Sciences, E Floor, Medical School, Queen's Medical Centre, University of Nottingham, Nottingham, NG72UH, UK. Fax: +115-9709259.
E-mail address: christine.norman@nottingham.ac.uk (C. Norman).

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conditioning in PE groups. The AMP doses were the same as those used in Norman and Cassaday (2003) and Killcross et al. (1994).

All procedures were carried out under the United Kingdom Animals (Scientific Procedures) Act 1986 and Project Licence number PPL 40/2019.

Animals. Fourty-eight male Wistar rats of mean weight 233 g (SEM = 1.55) were used. Food was rationed to approximately 15 g of lab chow (B&K Universal, UK) per rat per day (fed in pairs) and given at the end of each day's testing. Water was available ad libitum in the home cage.

Apparatus. Details of apparatus have been described elsewhere (Norman & Cassaday, 2003), the only difference being that the water spout was here replaced by a food magazine. Briefly, six automated conditioning chambers (Cambridge Cognition, UK) were used, with a food magazine set into one wall. A light constantly illuminated the magazine during any session where food was available (therefore, not during extinction). The magazine had a clear Persex flap across the entrance and responses were measured by the breaking of a photobeam as it was pushed open.

The unconditioned stimulus (UCS) was 2×45 mg sucrose pellets (Noyes precision pellets, Formula F, Sandown Scientific, UK). The contextual stimulus to which animals were conditioned was a set of four continuously flashing lights (three mounted on the same wall as the food magazine plus the house light) flashing both on and off for 0.5 s.

Drugs D-Amphetamine sulphate (Sigma, UK) was dissolved in physiological saline to a volume of 1 mg/kg and administered by intra-peritoneal injection. Drug doses (expressed as weight of salt) were 0.5 mg/kg AMP, 1.5 mg/kg AMP and saline vehicle and were administered 15 min prior to each session of pre-exposure and conditioning. Extinction and baseline were both conducted drug free.

Design and statistical analysis. Rats were divided into six experimental conditions ($n = 8$) in a 3×2 factorial design for analysis of variance (ANOVA). Between subjects factors were Drug (at levels saline, 0.5 mg/kg AMP and 1.5 mg/kg AMP) and Pre-exposure (at levels PE and NPE). In baseline and acquisition there was also a repeated measures factor of days (at 2 and 15 levels respectively). Planned comparisons were conducted by *t* test.

Procedure. Rats were handled for 10 min per day for 10 days prior to experimental procedures.

Baseline. Rats were individually shaped to nosepoke into the food magazine for sucrose pellets in 2×5 min sessions over 2 days. There then followed two days of baseline measures with 10 unsignalled sucrose deliveries on a variable interval schedule over a 10 min session. The total number of magazine entries was recorded.

Pre-exposure. There were 3 days of 30 min sessions of pre-exposure. Half the rats in each drug condition were pre-exposed to the continuously flashing lights (PE groups) and the other half placed in the conditioning chamber in the absence of the experimental stimulus (NPE groups). There were no sucrose deliveries and the magazine light was not illuminated, nor were any responses recorded.

Acquisition. Conditioning consisted of 15 days of a 30 min session with the flashing light stimulus continuously presented to all experimental groups. There were 10 variable interval unsignalled deliveries of sucrose pellets. Responding was recorded as total magazine entries during the session, except for the 5 s following food delivery, which were recorded separately ('Post-UCS') in order to measure drug effects on collection of the food UCS.

Extinction. There was one 30 min extinction session comprised of continuous presentation of the flashing lights in the absence of any sucrose delivery for all experimental groups. Responses were recorded as total magazine entries.

It was predicted that in controls conditioning to the contextual stimulus would be greater in those rats not pre-exposed to that stimulus, but that this difference would be reduced under AMP. The difference between groups was in fact reduced or abolished under both doses of AMP, though for different reasons.

Baseline. Groups were evenly matched prior to conditioning. Although there was an effect of Days, $F(1,42) = 4.7$, $p < .05$ with greater responding on day 2 than day 1; mean (SEM): day 1 = 118(9); day 2 = 139(8), there were no effects of prospective Drug or Pre-exposure condition or their interactions, $F_{\max}(2,42) = 1.7$.

Acquisition—total magazine entries. There was a main effect of Drug, $F(2,42) = 9.05$, $p < .001$, with greater responding in the saline and 0.5 mg/kg AMP conditions than the 1.5 mg/kg AMP condition, $t(30) = 2.64$, $p < .01$ and $t(30) = 4.63$, $p < .001$, respectively. The overall Pre-exposure × Drug interaction did not reach significance, $F(2,42) = 2.7$, $p = .08$.

However, there was an effect of Days, $F(14,588) = 2.88$, $p < .001$ and a marginal Days × Pre-exposure × Drug interaction, $F(28,588) = 1.46$, $p = .06$. As Fig. 1 demonstrates this interaction arose because there was a clear LI effect for the saline controls (lower responding in PE than NPE rats) in the absence of such an effect at either AMP dose. *t* Tests confirmed that the difference between PE and NPE groups was only significant for saline controls (on many of the conditioning sessions: days 2, 3, 8, 11, 13, 14, and 15; $t_{\min}(14) = 2.09$, $p < .05$ on day 8). The loss of LI under AMP was seen at two levels of responding, in that for the 0.5 mg/kg AMP dose both groups responded as highly as the saline NPE group, whereas for the 1.5 mg/kg AMP dose the response rate in both groups was lower.

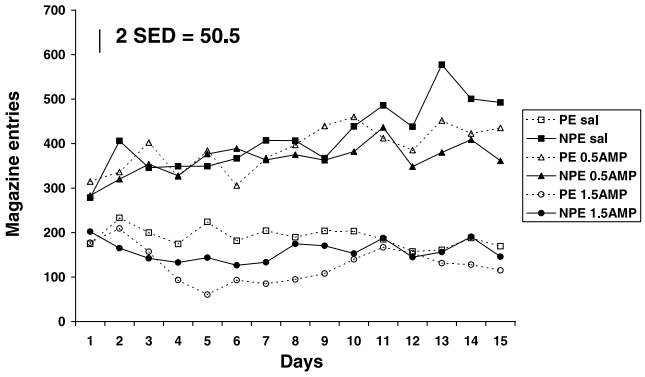

Fig. 1. Mean number of magazine entries (for saline, 0.5 and 1.5 mg/kg D-amphetamine) during presentation of the flashing light (contextual) stimulus over the 15 days acquisition. Dotted lines with open symbols represent pre-exposed (PE) groups and solid line with closed symbols non-pre-exposed (NPE) groups. Bar at top left (2 SED) shows 2 standard errors of the difference of the means.

Post-UCS responding. Responding during the Post-UCS period was analysed to ensure that the UCS was collected. The only difference between groups was a main effect of Drug, $F(2,42) = 4.68$, $p < .05$, with reduced responding in the 1.5 mg/kg AMP condition compared with the 0.5 mg/kg AMP and saline conditions, $t(30) = 2.87$, $p < .01$ and $t(30) = 2.11$, $p < .05$, respectively. However, the means per day were always greater than the number of UCS presentations in all groups, (lowest mean (SEM) being day $1 = 12(1.47)$ entries in the 1.5 mg/kg AMP condition) indicating that despite the lower response rate in 1.5 mg/kg AMP groups, the UCS was being collected. Therefore, the reduced response rate should not have prevented learning.

Extinction—total magazine entries. There was an effect of Drug, $F(2,42) = 6.29$, $p < .01$ and a Drug × Pre-exposure interaction, $F(2,42) = 5.14$, $p < .01$ but no overall effect of PE, $F(1,42) = 2.8$, $p = .1$. As Fig. 2 shows the interaction arose because of a clear LI effect in controls, $t(14) = 2.44$, $p < .05$, but no such effect with either AMP dose, both ts < 1. As extinction is drug free, this result confirms the effect seen under drug in acquisition.

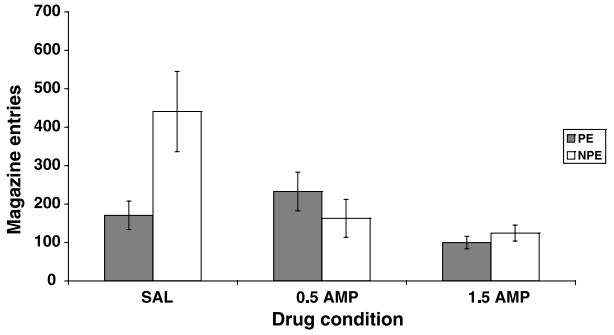

Fig. 2. Mean number of magazine entries (for prior drug condition; saline, 0.5 and 1.5 mg/kg D-amphetamine) during presentation of the flashing light stimulus. Grey bars represent pre-exposed (PE) groups and white bars non-pre-exposed (NPE) groups. Error bars represent 2 standard errors of the group mean.

Systemic AMP disrupted acquisition of LI to a contextual stimulus at two doses and levels of responding. At the lower dose this disruption arose from increased responding in the PE group and at the higher dose from reduced responding in the NPE group (compared with controls). Reduced responding at the higher dose may have resulted from stereotypical behaviour sometimes seen with repeated administration at this dose (Robinson & Becker, 1986).

There was a difference in the pattern of responding between acquisition and extinction for the 0.5 mg/kg AMP condition. In acquisition, LI was abolished because responding was as high in both PE and NPE 0.5 mg/kg AMP groups as for NPE controls. In extinction, the difference between NPE and PE groups under AMP was also lost, but in this case it was because of reduced responding in all drug groups compared with NPE controls (cf. Figs. 1 and 2). However, lower levels of responding for drug conditions than controls are to be expected in extinction due to the state-dependent effect of the absence of drug (Overton, 1964). Thus, in extinction interpretation of the pattern of responding is less clear, in that the loss of LI could be attributed to state-dependent effects of the drug, although the response levels remain high enough to demonstrate learning.

The loss of LI to an experimental contextual stimulus here extends the findings of AMP disruption of LI to discrete stimuli, (e.g. Killcross et al., 1994; Weiner & Feldon, 1997) to that of a contextual stimulus. It could be argued that aspects of this procedure (in particular the pre-exposure of the contextual stimulus in the absence of food, following magazine training) might introduce confounds such as conditioned inhibition (CI). In principle, this kind of objection applies to any LI procedure where some baseline response must first be established. However, LI procedures are different from those conventionally used for CI (in which reinforced CS presentations are interspersed with non-reinforced presentations of CS plus CI).

In summary, amphetamine has disrupted LI to a contextual stimulus in an appetitive procedure (which despite their advantages have rarely been used to study LI) and at doses that disrupt LI to discrete stimuli. To the extent that this flashing light represents a context, this finding therefore extends the effects of AMP on discrete stimuli to that of contextual stimuli. However, the nature of this flashing light stimulus as a functioning context needs to be further explored, perhaps by testing a multi-modal experimental stimulus in the same procedure.

This finding has implications for our understanding of AMP effects on LI to discrete stimuli, in that LI is known to be highly context dependent. It follows that treatments that abolish LI may do so in part because of an increase in contextual conditioning. The present study suggests a possible mechanism for this effect (but see Weiner, Lubow, & Feldon, 1984, 1988).

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